Agency Response Letter GRAS Notice No. GRN 000242

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CFSAN/Office of Food Additive Safety

October 14, 2008

Robert S. McQuate, Ph.D.
GRAS Associates, LLC
20482 Jacklight Lane
Bend, OR 97702-3074

Re: GRAS Notice No. GRN 000242

Dear Dr. McQuate:

The Food and Drug Administration (FDA) is responding to the notice, dated January 18, 2008, that you submitted on behalf of Neptune Technologies and Bioressources (Neptune) in accordance with the agency's proposed regulation, proposed 21 CFR 170.36 (62 FR 18938; April 17, 1997; Substances Generally Recognized as Safe (GRAS); the GRAS proposal). FDA received the notice on February 4, 2008, filed it on February 4, 2008, and designated it as GRAS Notice No. GRN 000242.

The subject of the notice is krill oil. The notice informs FDA of the view of Neptune that krill oil is GRAS, through scientific procedures, for use as a direct food ingredient in various foods as described in Table 1 (below). Neptune views this use of krill oil to be "as an alternative or substitute for fish oil."

Table 1. Neptune's intended conditions of use

Food	Milligrams (mg) Per Serving
Breakfast Cereals	300
Cheese	300
Beverages (Nonalcoholic)	150-200
Fruit Juices	150-250
Frozen Dairy Desserts	300-500
Milk Products	300-500
Medical Foods	300-500

As part of its notice, the notifier includes the findings of a panel of individuals (Neptune's GRAS panel) who evaluated the data and information that are the basis for the notifier's GRAS determination. Neptune considers the members of its GRAS panel to be qualified by scientific training and experience to evaluate the safety of substances added to food. Neptunes's GRAS panel evaluated estimates of dietary exposure, method of production, and product specifications as well as published and unpublished studies. Neptune's GRAS panel concludes that krill oil produced in accordance with good manufacturing practices is considered to be generally recognized as safe when used as a substitute for fish oils.

Krill oil is obtained from krill which are small, pelagic, shrimp-like crustaceans of the family Euphausiidae. Krill oil is a reddish, opaque, lipid extract of marine krill (*Euphasia superba*). The major components of krill oil are triglycerides and phospholipids, and include the fatty acids eicosapentaenoic acid (EPA, C20:5 n–3), docosahexeanoic acid (DHA, C22:6 n–3), and *cis*-11-octadecenoic acid (vaccenic acid, C18:1 n–7). The combined concentration of EPA and DHA in krill oil is approximately 26 percent, with a ratio of EPA to DHA of approximately 2:1. Krill oil also contains naturally-occurring esterified astaxanthin.

Neptune describes the manufacturing process for krill oil. Frozen Antarctic krill are crushed and the lipids and proteins are extracted using acetone. Following extraction, the krill proteins and lipids are filtered through an organic solvent-resistant filter under reduced pressure to enable physical separation of lipids and proteins. Excess acetone is evaporated and water is separated from the oil. The oil is subjected to additional filtration and purification to remove impurities and is packaged in a modified nitrogen-containing atmosphere and stored. The notifier provides product specifications for krill oil, including specifications for fatty acids, total phospholipids, esterified astaxanthin, saturated fatty acids, and trans-fat (<0.1 percent). Specifications also include limits on residual acetone (<10 milligrams per kilogram (mg/kg), lead (<0.1 mg/kg), mercury (<0.1 mg/kg), arsenic (<0.1 mg/kg), cadmium (<0.1 mg/kg), pesticides, and microbiological contaminants.

Neptune calculates an estimated daily intake (EDI) of krill oil based on minimum and maximum use levels listed in Table 1 and reported food consumption data from the 1994-1996, and 1998 USDA Continuing Survey of Food Intakes by Individuals (CSFII). Neptune reports the mean EDI as 3.1 to 4.1 grams per person per day (g/p/d) and the 90th percentile EDI (mean multiplied by two) as 6.2 to 8.3 g/p/d. Neptune notes that at a combined level of 26 percent of total EPA and DHA, the maximum daily consumption of EPA and DHA would be 2.2 g/p/d. Neptune states that the maximum expected daily consumption of EPA and DHA from krill oil is within the recommended intake for menhaden oil (less than 3 g/p/d).[1]

Neptune discusses FDA's recommendations regarding safe levels of exposure to EPA and DHA, noting that krill oil is intended as an alternative or substitute for fish oil. Consequently, dietary intake of total EPA and DHA from krill oil will be substitutional and not additive to that which would be ingested from fish oil. Neptune also notes that the use levels of krill oil in foods will be self-limiting due to the strong taste that begins to be detected at use levels between 300 and 500 milligrams per serving, depending on the type of food.

In its discussion of the safety of krill oil, Neptune provides a compositional comparison between krill oil and other marine-derived oils in the marketplace, including menhaden oil, tuna oil, salmon oil, and anchovy oil. Neptune concludes that the composition of krill oil is similar to marine oils commonly consumed. Neptune also summarizes the results of published and unpublished studies supporting the safe use of krill oil in foods. Neptune describes published rodent and human clinical studies examining nutritional and clinical utility, which also provided evidence that krill oil was well-tolerated. Neptune discusses results from an unpublished human clinical study as well as an unpublished rodent study that corroborates Neptune's conclusion regarding the safe use of krill oil in food. Neptune also provides a discussion of the evidence supporting the safety of the krill oil components astaxanthin and vaccenic acid concluding that the presence of these substances does not affect the safety of krill oil.

Allergen Labeling

The Food Allergen Labeling and Consumer Protection Act of 2004 (FALCPA) amends the Federal Food, Drug, and Cosmetic Act (FFDCA) to require that the label of a food that is or contains an ingredient that bears or contains a "major food allergen" declare the presence of the allergen (section 403(w)). FALCPA defines a "major food allergen" as one of eight foods or food groups (i.e., milk, eggs, fish, Crustacean shellfish, tree nuts, peanuts, wheat, and soybeans) or a food ingredient that contains protein derived from one of those foods. Issues associated with labeling food are the responsibility of the Center for Food Safety and Applied Nutrition's Office of Nutritional Products, Labeling, and Dietary Supplements.

Standards of Identity

In the notice, Neptune states its intention to use krill in several food categories, including foods for which standards of identity exist located in Title 21 of the Code of Federal Regulations. We note that an ingredient that is lawfully added to food products may be used in a standardized food only if it is permitted by the applicable standard of identity.

Potential Requirement for a Color Additive Petition

FDA notes that krill oil has the potential to impart color in food products that contain it. As such, the use of krill oil in food products may constitute the use of a color additive under section 201(t)(1) of the FFDCA and FDA's implementing regulations in 21 CFR Part 70. Under section 201(t)(1) and 21 CFR 70.3(f), the term color additive means a material that is a dye, pigment, or other substance made by a process of synthesis or similar artifice, or extracted, isolated, or otherwise derived from a vegetable, animal, mineral, or other source, and that is capable (alone or through reaction with another substance) of imparting color when added or applied to a food; except that such term does not include any material which the Secretary,(2) by regulation, determines is used (or intended to be used) solely for a purpose or purposes other than coloring. Under 21 CFR 70.3(g), a material that otherwise meets the definition of color additive can be exempt from that definition on the basis that it is used or intended to be used solely for a purpose or purposes other than coloring, as long as

the material is used in a way that any color imparted is clearly unimportant insofar as the appearance, value, marketability, or consumer acceptability is concerned. Given the construct of section 201(t)(1) of the FFDCA and 21 CFR 70.3(f) and (g), the use of a substance that is capable of imparting color may constitute use as a color additive in addition to use as a food additive or GRAS substance. For example, beta-carotene is both approved for use as a color additive (21 CFR 73.95) and affirmed as GRAS for use as a nutrient supplement (21 CFR 184.1245); in some food products, beta-carotene is used for both purposes. Importantly, if the use of krill oil constitutes use as a color additive within the meaning of section 201(t)(1) of the FFDCA and FDA's implementing regulations in 21 CFR 70.3(f) and (g), section 721(a) of the FFDCA requires premarket review and approval of that use by FDA. Under section 402(c) of the FFDCA, a food product that contains an unapproved color additive would be deemed adulterated.[3]

Medical Foods

In its notice, Neptune informs FDA that one intended use of krill oil is use in medical foods. Section 5(b) of the Orphan Drug Act (ODA) defines a medical food as a food that is formulated to be consumed or administered enterally under the supervision of a physician and that is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation. Section 403(q) of the FFDCA lays out the statutory framework for nutrition labeling of food products. Section 403(r) of the FFDCA lays out the statutory framework for health claims and nutrient content claims. Under section 403(q)(5)(A)(iv) of the FFDCA and FDA's implementing regulations in 21 CFR 101.9(j)(8), the requirements for nutrition labeling do not apply to medical foods as defined in section 5(b) of the ODA. Under section 403(r)(5)(A) of the FFDCA and FDA's implementing regulations in 21 CFR 101.13(q)(4)(ii) and 21 CFR 101.14(f)(2), the requirements for nutrient content claims and health claims, respectively, do not apply to medical foods as defined in section 5(b) of the ODA. For your information, FDA's response to Neptune's notice that krill oil is GRAS for use in medical foods does not address the question of whether any particular food product that contains krill oil as an ingredient would be a medical food within the meaning of section 5(b) of the ODA and, thus, would be exempt from the requirements for nutrition labeling, nutrient content claims, and health claims.

Section 301 (ll) of the FFDCA

Section 301(ll) of the FFDCA prohibits the introduction or delivery for introduction into interstate commerce of any food that contains a drug approved under section 505 of the FFDCA, a biological product licensed under section 351 of the Public Health Service Act, or a drug or a biological product for which substantial clinical investigations have been instituted and their existence made public, unless one of the exemptions in section 301(ll)(1)-(4) applies. In its review of Neptune's notice that krill oil is GRAS for use in certain foods, FDA did not consider whether section 301(ll) or any of its exemptions apply to foods containing krill oil. Accordingly, this response should not be construed to be a statement that foods that contain krill oil, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information provided by Neptune, and other information available to FDA, the agency has no questions at this time regarding Neptune's conclusion that krill oil is GRAS under the intended conditions of use. The agency has not, however, made its own determination regarding

the GRAS status of the subject use of krill oil. As always, it is the continuing responsibility of Neptune to ensure that food ingredients that the firm markets are safe, and are otherwise in compliance with all applicable legal and regulatory requirements.

In accordance with proposed 21 CFR 170.36(f), a copy of the text of this letter responding to GRN 000242, as well as a copy of the information in this notice that conforms to the information in the proposed GRAS exemption claim (proposed 21 CFR 170.36(c)(1)), is available for public review and copying on the homepage of the Office of Food Additive Safety (on the Internet at http://www.cfsan.fda.gov/~lrd/foodadd.html).

Sincerely,

Laura M. Tarantino, Ph.D.
Director
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition

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(1)FDA has affirmed the GRAS status of menhaden oil for use as a direct food ingredient (21 CFR 184.1472) provided that the combined intake of EPA and DHA from consumption of menhaden oil does not exceed 3 g/p/d. FDA had raised concerns about the consumption of high levels of EPA and DHA and possible adverse effects of consumption on bleeding time, glycemic control, and low-density lipoprotein cholesterol levels (62 FR 30751 at 30757; June 5, 1997). FDA subsequently revised the menhaden oil rule to reallocate the uses of menhaden oil in conventional food, while maintaining the 3 g/p/d limit on EPA and DHA, and to require that menhaden oil not be used as an ingredient in foods in combination with another added oil that is a significant source of EPA and DHA (70 FR 14530; March 23, 2005).

(2)The Secretary of the Department of Health and Human Services.

(3) We note that section 721(b)(4) of the FFDCA provides that a color additive shall be deemed to be safe and suitable for the purpose of listing under section 721(b) of the FFDCA while there is in effect a published finding of the Secretary declaring that the substance is exempt from the definition of "food additive" because of its being generally recognized by qualified experts as safe for its intended use as provided in section 201(s) of the FFDCA. Importantly, FDA's response to GRN 000242 does not constitute a "finding of the Secretary" within the meaning of section 721(b)(4) of the FFDCA.

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